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(54) Title: **ION-STRENGTH INDEPENDENT SUSTAINED RELEASE PHARMACEUTICAL FORMULATION**

(57) Abstract: The present invention is related to an optionally coated pharmaceutical hydrophilic gel forming matrix formulation comprising one or more active substances and having a prolonged release of said one or more active substances upon exposure to gastrointestinal fluids, characterized in that said release is substantially ion-strength independent. The invention is further related to a method of preparing this formulation which can be used in the administration of active substances for the treatment of a large number of disorders.

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Ion-strength independent sustained release pharmaceutical formulation

The present invention is related to a pharmaceutical formulation with a substantially sustained release behavior which is independent of the ion-strength of the dissolution medium, e.g. the gastrointestinal fluid. The sustained release is achieved over a time period up to 16 hours. The dosage form combines one or more active substances with a mixture of hydrophilic polymer carriers resulting in a gel forming matrix formulation.

Hydrophilic gel forming matrix formulations are well known dosage forms to control the dissolution behavior of active substances. The mechanism by which the active substance is released, starts with the hydration of the dosage form surface to form a gel structure. Simultaneously the active substance at the formulation surface dissolves in the dissolution medium. In the stationary phase, the dissolution medium continuously penetrates the gel structure and the gel expands. The active substance dissolves in the dissolution medium and is transported to the outer layer of the gel. Meanwhile, erosion of the outer layers of the gel occurs. Finally the release levels off, caused by the decreased concentration gradient of the active substance in the formulation and the penetrated dissolution medium. This mechanism is described in the prior art, e.g. Manford Robinson, The Theory and Practice of Industrial Pharmacy, 2nd edition, Chapter 14: "Sustained Action Dosage Forms".

Hydrophilic polymers used in the above described formulations are mostly polysaccharide carriers such as the cellulose derivatives hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), hydroxyethylcellulose (HEC), sodium carboxymethylcellulose (NaCMC) or combinations of these cellulose derivatives.

Formulations of these type are described in numerous patents and patent applications, e.g. in US 4,871,548 and EP-A-0923934.

US 4,871,548 discloses a controlled release dosage form comprising an active compound and a mixture of at least a low viscosity cellulose ether and a high viscosity cellulose ether. EP-A-0923934 discloses a modified release matrix formulation of cefaclor and cephalexin comprising 5-35% of a mixture of hydrophilic polymers of different grades, wherein the hydrophilic polymers comprise about 0.1% to about 20% by weight of medium viscosity hydroxypropyl methylcellulose and about 0.1% to about 20% of low viscosity hydroxypropylcellulose.

Although the above mentioned formulations are described as sustained release formulations in general, this sustained release only appears when the concentration of salts, the ion-strength, in the dissolution medium is low. The release rate of the active substance from the above mentioned formulation may be substantially dependent on the ion-strength. A high ion-strength may even lead to so-called dose-dumping. In this case the total amount of active substance is released in a very short time, which may lead to undesired, and even dangerous high blood levels of the active substance. A high ion-strength often occurs direct after taking a meal. As patients often take their medication just after a meal there is a high risk that ion-strength dependent formulations give rise to unwanted fast release of active substance instead of the desired sustained release.

WO 98/47491 describes a sustained release formulation wherein the control of the release of the active substance is based on a combination of two so called 'intelligent' polymers, having opposing wettability characteristics, one demonstrating a stronger tendency towards hydrophobicity and the other a stronger tendency towards hydrophilicity. In this formulation dose dumping can only be prevented by coating with an enteric coating.

It is the objective of the present invention to provide a sustained release formulation which is substantially independent from the ion-strength of the dissolution medium, which is normally the gastrointestinal fluid even when the formulation is not coated.

It is obvious for a person skilled in the art that the formulation should also meet the normal physical and pharmaceutical requirements in the art, such as good flowing properties of the powder during tableting, a crushing strength of compressed tablets of at least 30 N, a friability below 1 % at a compression force between 10 and 40 KN, uniformity of content and sufficient stability. Further it is a requirement that the formulation can be prepared using normal formulation procedures and equipment, so that no large investments are necessary.

This objective can be achieved, according to the present invention, by a pharmaceutical hydrophilic gel forming matrix formulation having a prolonged release of one or more active substances upon exposure to gastrointestinal fluids, characterized in that said release is substantially ion-strength independent.

Prolonged release is defined as a (gradual) release of the active substance from the dosage form over a time period of 45 minutes or more. This period starts usually with

the administration of the dosage form, or with the start of in-vitro dissolution test (the moment the dosage form is brought into the dissolution medium).

By the term substantially ion-strength independent is meant that the release rate
5 profile of the active substance is not significantly changed (according to General
Chapter 711: Physical tests and Determinations in USP 24 ($\pm 10\%$ of label claim))
when the ion strength (I) is varied between 0.05 and 0.45 mol/l . The ion strength (I)
is defined as $I = \frac{1}{2} \sum c_i z_i^2$, in which c is the concentration of the different ions in the
solution and z_i their respective charge number (Handbook of Chemistry and Physics
10 71st edition, David R. Lide ed., page 2-18, Boston, CRC Press Inc.; 1990-1991).

Although a coating is not essential to achieve the independency of the ion-strength,
the formulation is optionally coated with a coating material in order to achieve
another desired effect, such as masking of the taste or application of color. Suitable
15 coating materials are known in the art and are for example HPMC, acrylics,
ethylcellulose (see Graham Cole ed., Pharmaceutical Coating Technology, London,
Taylor & Francis Ltd.; 1995)

The hydrophilic gel forming matrix has the form of tablets or of a multi-particulate
20 dosage form and preferably contains a mixture of at least two hydrophilic high
viscosity cellulose ethers. Although the presence of a hydrophobic cellulose ether
such as ethylcellulose will normally have no detrimental effect on the release
properties of the present formulation, preferably no substantial amount of said
hydrophobic cellulose ether is present. With a substantial amount of hydrophobic
25 cellulose ether is meant an amount greater than 20% of the total weight of the gel
forming polymers.

Cellulose ethers are well known in the art and are available in pharmaceutical grades
and with different average molecular weights leading to different viscosities of a
30 solution of these cellulose ethers. For the purpose of this patent application,
hydrophilic polymers may be characterized by their viscosities in a 2% w/w aqueous
solution as low viscosity (less than about 1000 mPas), medium viscosity (about 1000
mPas to about 10,000 mPas) and high viscosity (greater than about 10,000 mPas)

35 Hydrophilic hydroxypropyl methylcellulose polymers (HPMC's) which may be used in
the present invention are available in different viscosity grades from Dow Chemical

Co. under the brand name Methocel® and from Shin Etsu under the brand name Metolose®.

5 Examples of low viscosity polymers are Methocel E5®, Methodcel E-15LV®, Methocel E50LV®, Methocel K100LV® and Methocel F50LV®, whose 2% aqueous solutions at 25°C have viscosities of 5 mPas, 15 mPas, 50 mPas, 100 mPas and 50 mPas, respectively.

Examples of medium viscosity HPMC's are Methocel E4M® and Methocel K4M, whose 2% aqueous solutions at 25°C have viscosities of 4000 mPas.

10 Examples of high viscosity HPMC's are Methocel K15M® and Methocel K100M® whose 2% aqueous solutions at 25 C have viscosities of 15,000 mPas and 100,000 mPas.

15 Hydrophilic hydroxyethylcellulose polymers (HEC's) which may be used in the present invention are available in different viscosity grades from AQUALON under the brand name Natrosol® and from Amerchol Corporation under the brand name Cellosize®.

Examples of low viscosity polymers are Natrosol L® en Natrosol J®, whose 2% aqueous solutions at 25 °C have viscosities of 10 mPas and 20 mPas, respectively.

20 Examples of medium viscosity polymers are Natrosol G® and Natrosol K® whose 2% aqueous solutions at 25 °C have viscosities of 200 mPas and 1500 mPas, respectively.

Examples of high viscosity polymers are Natrosol M® and Natrosol HH® whose 2 % aqueous solutions have viscosities at 25 °C of 4000 mPas and 90000 mPas, respectively.

25 In a preferred embodiment of the present invention the formulation comprises a mixture of a high or medium viscosity hydroxypropylmethylcellulose (HPMC) and a high or medium viscosity hydroxyethylcellulose (HEC), The ratio between the high or medium viscosity HPMC and the high or medium viscosity HEC is 1/0.85 to 1/1.2, preferably is 1/0.9 to 1/1.1, even more preferably is 1/0.95 to 1/1.05 and most preferred is 1/1. The formulation optionally may comprise a low viscosity HPMC. In
30 that case the ratio between high or medium viscosity HPMC and low viscosity HPMC is in the range between 1/0.01 and 1/0.2 and preferably is between 1/0.01 and 1/0.1 and even more preferably is between 1/0.02 and 1/0.05.

35 It has surprisingly been found that formulations having the above mentioned composition can be used to prepare tablets that have a release rate that is

independent of the ion-strength in the range that is normal in the gastro-intestinal fluid. Said normal range is between 0.17 and 0.35 mol/L.

5 Apart from its independence from the ion-strength, the release controlling principle of the formulation is also substantially independent from the pH in the range between pH = 1.3 and pH = 7.4. This means that the release rate of active substance is not influenced by the pH in those cases where the active substance release is not limited by the solubility of the active substance substance, i.e. that the differences in release values (in %) at a given point in time are less than 20% of the label claim (see 10 Chapter Dissolution Specifications (page 1080-81) in FIP Guidelines for Dissolution Testing of Solid Oral Products (Final Draft, 1995), Drug Information Journal 1996, Vol 30, 1071-84) within the whole pH range between 1.3 and 7.4.

15 Because of its optimal properties as a sustained release formulation, the formulation according to the present invention can be used in the treatment of a large series of diseases in the case that sustained release properties are desirable. Examples of active substances that can be formulated into a sustained release formulation are active substances for the treatment of CNS disorders, including schizophrenia, episodic paroxysmal anxiety (EPA) disorders such as obsessive compulsive disorder 20 (OCD), post traumatic stress disorder (PTSD), phobia and panic, major depressive disorder, bipolar disorder, Parkinson's disease, general anxiety disorder, autism, delirium, multiple sclerosis, Alzheimer disease/dementia and other neurodegenerative diseases, severe mental retardation and dyskinesias, such as Huntington's disease or Gilles de la Tourette's syndrome, anorexia, bulimia, stroke, 25 addiction/dependency/craving, sleep disorder, epilepsy, migraine; attention deficit/hyperactivity disorder (ADHD); cardiovascular diseases including heart failure, angina pectoris, arrhythmias, myocardial infarction, cardiac hypertrophy, hypotension, hypertension – e.g. essential hypertension, renal hypertension, or pulmonary hypertension, thrombosis, arteriosclerosis, cerebral vasospasm, 30 subarachnoid hemorrhage, cerebral ischemia, cerebral infarction, peripheral vascular disease, Raynaud's disease, kidney disease – e.g. renal failure; dyslipidemias; obesity; emesis; gastrointestinal disorders including irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), gastroesophageal reflux disease (GERD), motility disorders and conditions of delayed gastric emptying, such as postoperative or 35 diabetic gastroparesis, and diabetes, ulcers – e.g. gastric ulcer; diarrhoea; other diseases including osteoporosis; gynecological disorders, inflammations; infections such as bacterial, fungal, protozoan and viral infections, particularly infections caused

by HIV-1 or HIV-2; pain; cancers; chemotherapy induced injury; tumor invasion; immune disorders; urinary retention; asthma; allergies; arthritis; benign prostatic hypertrophy; endotoxin shock; sepsis; complication of diabetes mellitus.

Preferred active substances to be formulated are active substances that are used for the treatment of CNS disorders, such as fluvoxamine (5-methoxy-1-[4-(trifluoromethyl)phenyl]-1-pentanone O-(2-aminoethyl)oxime) or flesinoxan ((+)-benzamide, N-[2-[4-[(2R)-2,3-dihydro-2-(hydroxymethyl)-1,4-benzodioxin-5-yl]-1-piperazinyl]ethyl]-4-fluoro), for the treatment of cardiovascular disorders, such as tedisamil (N,N'-dicyclopropylmethyl-9,9-tetramethylene-3,7-diazabicyclo[3.3.1]-nonane) or propranolol or active substances that are used in the treatment of gynecological disorders e.g. in Hormone Replacement Therapy, such as dydrogesterone, estradiol or conjugated estrogens. The present invention is especially useful for the formulation of the active substance flesinoxan, especially as its monohydrochloride ((+)-benzamide, N-[2-[4-[(2R)-2,3-dihydro-2-(hydroxymethyl)-1,4-benzodioxin-5-yl]-1-piperazinyl]ethyl]-4-fluoro-monohydro-chloride), described in EP0138280 and EP307061 and for tedisamil, preferably as its sequifumarate (N,N'-dicyclopropylmethyl-9,9-tetramethylene-3,7-diazabicyclo-[3.3.1]-nonane 1.5 hydrogenfumarate), described in EP 0550383.

The present invention also relates to a method of preparing a formulation as described above, characterized in that

- (1) a core is compressed of a mixture comprising one or more active substances and a mixture of at least two hydrophilic high or medium viscosity cellulose ethers yielding a substantially ion-strength independent and prolonged substantially zero-order release of active substances; and
- (2) the core is optionally coated.

The ingredients HPMC, HEC, active substance, pigment blend and glidant are mixed in a suitable mixer. This powder mixture is blended with sodium stearyl fumarate in a suitable mixer.

The active substance may be added in the form of a pregranulate to the powder mixture used to compress. Alternatively the powder mixture for tableting may be produced by a mixing procedure that is followed by a (wet or dry) granulation process.

The mixture of ingredients is compressed into tablets with commercial available equipment (e.g. a Courtoy® R0) using flow regulating agents like colloidal silica and lubricating agents like talcum, sodium stearyl fumarate or magnesium stearate. The

quantity of hydrophilic celluloses in the complete formulation ranges between 15% and 99.5 %, while the amount of active substance ranges between 0.1% and 80%. The amount of flow regulating and lubricating agent is fixed to improve powder flow properties and to prevent sticking of powder to the dye walls or the punches. The amount of glidant is between 0.05% and 5% and is preferably about 0.2%. The amount of lubricant is between 0.05% and 5% and is preferably about 0.4 %. For commercial reasons, the powder mixture may be coloured with between 0.1% and 10% pigment blend. Typical pigment blends are commercially available, e.g. from COLORCON® as Opadry.®

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All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

15

The following examples are only intended to further illustrate the invention, in more detail, and therefore these example are not deemed to restrict the scope of the invention in any way.

Example 1. Preparation of an ion-strength independent formulation.**Example 1a. General procedure for the preparation**

First colloidal silica is passed through a sieve. Said sieve possesses preferably a
 5 screen between 0.40 mm and 0.595 mm. The active substance is mixed together
 with the hydrophilic celluloses, colloidal silica, pigment blend and if required mannitol
 in a suitable mixer. Said mixer is preferably a high shear mixer with the granulator in
 off position. The sodium stearyl fumarate is passed through a sieve. Said sieve
 possesses preferably a screen between 0.40 mm and 0.595 mm. The powder
 10 mixture is compressed into tablets with the desired dimensions. The compression
 equipment is preferably a rotary machine, like Korsch and Courtoy equipment.
 Optional, the tablets can be coated with water soluble celluloses or derivates of
 cellulose like ethylcellulose or acrylates based on aqueous suspensions or organic
 solvents. The coating process is preferably carried out in perforated drum equipment
 15 or with equipment based on fluidized bed technology.

Table 1. The composition of non-coated tablets (cores) , expressed in mg/tablet.

Materials	Flesinoxan Label claim: 2 mg/t	Acetamino- phen Label claim 2.2 mg/t	Fluvoxamine maleate Label claim: 100 mg/t	Tedisamil. di HCl Label claim: 100 mg/t	Tedisamil sesqui fumarate Label claim: 150 mg/t
Flesinoxan.HCl	2.18	n.a.	n.a.	n.a.	n.a.
Acetaminophen	n.a.	2.19	n.a.	n.a.	n.a.
Fluvoxamine maleate	n.a.	n.a.	100.00	n.a.	n.a.
Tedisamil.diHCl	n.a.	n.a.	n.a.	124.4	n.a.
Tedisamil.sesqui fum.	n.a.	n.a.	n.a.	n.a.	240.0
HPMC K4M	69.63	69.63	17.00	125.2	81.0
HPMC E5	7.50	7.50	12.50	20.0	14.0
HEC HX250PH	69.63	69.63	17.00	125.2	81.0
Mannitol SD200	n.a.	n.a.	100.00	n.a.	n.a.
Colloidal silica	0.30	0.30	0.50	1.60	4.0
Pigment blend PB23015	0.15	0.15	n.a.	0.40	n.a.
Sodium stearyl fumarate	0.60	0.60	3.00	3.20	5.0
Total tablet weight (mg)	150.00	150.00	250.00	400.00	425.00

n.a.: not applicable

Table 2. Properties of several compositions

Tablet property	Flesinoxan Label claim: 2 mg/t	Acetamino- phen Label claim 2.2 mg/t	Fluvoxamine maleate Label claim: 100 mg/t Coated	Tedisamil, diHCl Label claim: 100 mg/t	Tedisamil sesqui fumarate Label claim: 150 mg/t
Tablet dimension (mm)	5.5 x 11.0 mm Special shaped	7.0 mm round	8.0 mm round	8.0 x 15.0 mm oblong	8.0 x 15.0 mm oblong
Tablet weight (mg)	150	150	275	400	425
Crushing strength (N)	83	75	144	71	90
Friability (%)	not determined	not determined	not determined	0.4	0.05
Release profile	Table 4	Table 4	Table 4	Table 4	Table 4

Example 1b Release properties of several formulations

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The release of the active substance from the hydrophilic matrix tablets is measured in the USP apparatus II using paddles rotating at 50 rpm in either an USP dissolution buffer medium pH 6.8 of 0.05 molar (M), 0.17 M and 0.34 M prepared from di sodium hydrogen phosphate.2aq and citric acid.1aq (coded as F, G and H respectively) or in a half-change dissolution medium prepared from 0.1 M aqueous hydro chloride solution in the first part of the test (90 minutes) followed by 0.2 M pH 6.8 by adjusting with tri sodium phosphate.12 aq in the second part of the test. To increase the ionic strength of the aqueous solution during the test, sodium chloride is added to the solution. 1 liter dissolution medium of part two contains an amount of sodium chloride of respectively 0 gram (dissolution medium A), 10 gram (dissolution medium B), 15 gram (dissolution medium C), 30 gram (dissolution medium D1 and D2), and 50 gram (dissolution medium E1 and E2). In the dissolution media B, C, D1 and E1 the sodium chloride is only added in the second part of the test. In the dissolution media D2 and E2 75% of the sodium chloride is added in the first part of the test and 25% in the second part.

The release of the active substance is measured over 16 hours with sample intervals of one hour during the first two hours followed by sample intervals of two hours over the remaining test period. Samples may be analysed on-line with a HPLC system or by UV spectroscopy. The release of the different active compounds from the formulation is given in the tables 4a – 4c.

From the release data as given in the tables 4a-4c it can be concluded that the release of active substance from the formulation according to the present invention is substantially independent from the pH and the ion-strength, as differences in release values are less than 20%. Further it can be concluded that there is no substantial

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difference between the release profile when the ion-strength is increased at low pH (pH 1.2) and at higher pH (pH 6.8)

Table 3. Overview of dissolution media

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Dissolution method		Dissolution medium						
		A	B	C	D1	D2	E1	E2
1) pH 1.2	1.5 hours	750 ml 0.1 M HCl						
	NaCl added (g)					22.5		37.5
2) pH 6.8	14.5 hours	250 ml 0.2 M Na ₃ PO ₄ ·12aq						
	NaCl added (g)	0	10	15	30	7.5	50	12.5
Ion Strength (mol/L) in final dissolution medium		0.14	0.31	0.40	0.65	0.65	1.00	1.00

Dissolution method		Dissolution medium		
		F	G	H
pH 6.8	Na ₂ HPO ₄ ·2 aq + citric acid.1aq	0.05 M	0.17 M	0.34 M
Ion Strength (mol/L)		0.11	0.38	0.77

Table 4a. Release of several non-coated tablet compositions as function of time

Amount of active substance (%) Released after	Flesinoxan Label claim: 2 mg/t				Acetaminophen Label claim 2.2 mg/t			Fluvoxamine maleate Label claim: 100 mg/t		
	A	B	D1	E1	F	G	H	A	B	C
Dissolution medium										
0 hours	0	0	0	0	0	0	0	0	0	0
1 hour	20	18	20	18	21	15	25	22	22	22
2 hours	32	28	31	30	34	29	38	36	36	35
6 hours	59	52	53	50	70	63	70	67	66	64
16 hours	91	84	83	79	107	105	103	99	99	99

Table 4b. Release of several non-coated tablet compositions as function of time

Amount of active substance (%) Released after	Tedisamil.di HCl Label claim: 100 mg/t			Tedisamil sesqui fumarate Label claim 150 mg/t				
	A	B	C	A	D1	D2	E1	E2
Dissolution medium								
0 hours	0	0	0	2	0	0	2	0
1 hour	32	32	33	20	18	20	20	21
2 hours	50	51	52	32	24	32	32	33
6 hours	84	85	84	47	45	49	47	52
16 hours	92	94	93	79	75	76	75	81

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Table 4c. Release of tedisamil sesqui fumarate non-coated tablet in one single dissolution medium as function of time

Amount of active substance (%) Released after	Tedisamil.sesqui fumarate Label claim: 150 mg/t	
	750 ml 0.1 M HCl (pH 1.2)	750 ml 0.1 M HCl + 250 ml 0.2 M Na ₃ PO ₄ .12aq (pH 6.8)
Dissolution medium		
0 hours	0	0
1 hour	20	13
2 hours	33	22
6 hours	64	48
16 hours	97	89

Claims

1. A pharmaceutical hydrophilic gel forming matrix formulation comprising one or more active substances and having a prolonged release of said one or more active substances upon exposure to gastrointestinal fluids, characterized in that said release is substantially ion-strength independent.
2. A formulation according to claim 1, characterized in that said formulation is coated.
3. A formulation according to claims 1-2, characterized in that said hydrophilic gel forming matrix comprises as a carrier a mixture of a least two hydrophilic high or medium viscosity cellulose ethers.
4. A formulation according to claim 3, characterized in that said pharmaceutical formulation comprises high or medium viscosity hydroxypropylmethylcellulose (HPMC) and a high or medium viscosity hydroxyethylcellulose (HEC), in a ratio $HPMC/HEC = 1/0.85 - 1/1.2$ and optionally a low viscosity HPMC in a ratio high or medium viscosity HPMC/low viscosity HPMC = $1/0.01 - 1/0.2$.
5. A formulation according to claims 1-4, characterized in that said one or more active substances are selected from the group consisting of active substances for the treatment of CNS disorders, including schizophrenia, episodic paroxysmal anxiety (EPA) disorders such as obsessive compulsive disorder (OCD), post traumatic stress disorder (PTSD), phobia and panic, major depressive disorder, bipolar disorder, Parkinson's disease, general anxiety disorder, autism, delirium, multiple sclerosis, Alzheimer disease/dementia and other neurodegenerative diseases, severe mental retardation and dyskinesias, such as Huntington's disease or Gilles de la Tourette's syndrome, anorexia, bulimia, stroke, addiction/dependency/craving, sleep disorder, epilepsy, migraine; attention deficit/hyperactivity disorder (ADHD); cardiovascular diseases including heart failure, angina pectoris, arrhythmias, myocardial infarction, cardiac hypertrophy, hypotension, hypertension – e.g. essential hypertension, renal hypertension, or pulmonary hypertension, thrombosis, arteriosclerosis, cerebral vasospasm, subarachnoid hemorrhage, cerebral ischemia, cerebral infarction, peripheral vascular disease, Raynaud's disease, kidney disease – e.g. renal failure; dyslipidemias; obesity; emesis; gastrointestinal disorders including irritable bowel

syndrom (IBS), inflammatory bowel disease (IBD), gastroesophageal reflux disease (GERD), motility disorders and conditions of delayed gastric emptying, such as postoperative or diabetic gastroparesis, and diabetes, ulcers – e.g. gastric ulcer; diarrhoea; other diseases including gynecological disorders, osteoporosis; inflammations; infections such as bacterial, fungal, protozoan and viral infections, particularly infections caused by HIV-1 or HIV-2; pain; cancers; chemotherapy induced injury; tumor invasion; immune disorders; urinary retention; asthma; allergies; arthritis; benign prostatic hypertrophy; endotoxin shock; sepsis; complication of diabetes mellitus.

6. A formulation according to claim 5, characterized in that said active substance is an active substance for the treatment of CNS disorders.
7. A formulation according to claim 6, characterized in that said active substance is fluvoxamine or flesinoxan or a pharmaceutically acceptable salt thereof.
8. A formulation according to claim 7, characterized in that said active substance is flesinoxan monohydrochloride ((+)-benzamide, N-[2-[4-[(2R)-2,3-dihydro-2-(hydroxymethyl)-1,4-benzodioxin-5-yl]-1-piperazinyl]ethyl]-4-fluoro monohydrochloride).
9. A formulation according to claim 5, characterized in that said active substance is an active substance for the treatment of cardiovascular disorders.
10. A formulation according to claim 9, characterized in that said active substance is tedisamil or acetaminophen or a pharmaceutically acceptable salt thereof.
11. A formulation according to claim 10, characterized in that said active substance is tedisamil sesquifumarate (N,N'-dicyclopropylmethyl-9,9-tetramethylene-3,7-diazabicyclo[3.3.1]nonane 1.5 hydrogenfumarate)
12. A formulation according to claim 5, characterized in that said active substance is an active substance in Hormone Replacement Therapy.
13. A formulation according to claim 12, characterized in that said active substance is dydrogesterone, estradiol or conjugated estrogens.

14. A method of preparing a formulation according to claim 1-13, characterized in that
- (1) a core is compressed of a mixture comprising one or more active substances and a mixture of at least two hydrophilic high or medium viscosity cellulose ethers yielding a substantially ion-strength independent and prolonged substantially zero-order release of active substances; and
- 5 (2) the core is optionally coated.

INTERNATIONAL SEARCH REPORT

Int	Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, PAJ, EPO-Internal, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 47125 A (ANDRX PHARMACEUTICALS, INC.) 23 September 1999 (1999-09-23) page 2, line 36 -page 3, line 2 claims 1,6 ---	1,2,5
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Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

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